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Role of mitochondrial ROS in the brain: from physiology to neurodegeneration

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Abstract

Mitochondria are key organelles in the cell, which are responsible for energy production, and control many processes from signalling to cell death. The function of the mitochondrial electron transport chain is coupled with the production of reactive oxygen species (ROS) in the form of superoxide anion or hydrogen peroxide. Due to the constant production of ROS, mitochondria are protected by highly efficient antioxidant systems. The rapidly changing levels of ROS in mitochondria, coupled with multiple essential cellular functions, make ROS apt for physiological signalling. Thus mutations, environmental toxins and chronic ischaemic conditions could affect the mitochondrial redox balance and lead to the development of pathology. In long-living and non-mitotic cells like neurons, oxidative stress induced by overproduction of mitochondrial ROS or impairment of the antioxidant defence results in a dysfunction of mitochondria and initiation of the cell death cascade. Mitochondrial ROS overproduction and changes in mitochondrial redox homeostasis has been shown to be involved in a number of neurological conditions and in greater part of the neurodegenerative diseases. Here, we summarise the involvement of mitochondrial ROS in the mechanism of neuronal loss of major neurodegenerative disorders.

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Introduction

Mitochondria are organelles which play multiple important functions in the cell. Despite versatility of the duties, the main function of mitochondria is producing energy in form of ATP and almost all other processes inside of mitochondria are connected or dependent on bioenergetics. ATP synthesis by oxidative phosphorylation is coupled with mitochondrial respiration. Respiration is generating mitochondrial transmembrane potential by pumping the protons by mitochondrial complexes I, III and IV of electron transport chain (ETC). Mitochondrial membrane potential $\Delta\psi m$ is a cross linked element in mitochondrial function – it used as a proton motive force for ATP synthesis, help to maintain the shape of this organelle and keep mitochondrial pro-apoptotic proteins, which released to cytosol in case of $\Delta\psi m$ collapse.

Distribution of mitochondrial in the cells from diverse tissues is dependent on the energy demand. However, despite the density of mitochondria in myocytes is higher than in neurons, brain consumes almost 10 times more oxygen and glucose then other tissues. Considering high energy demand and high rate of ATP production and consumption in the brain most of mitochondrial mutations or mitochondrial toxins damage brain function and lead to neurological pathology [1].

Mitochondria produce free radicals, which due to high accessibility of the oxygen in this organelle are mostly reactive oxygen species (ROS). Although mitochondria produce ROS in number of enzymes, the vast majority of the free radicals which named in the literature “mitochondrial ROS” are produced in ETC. The rate of ROS production, mitochondrial membrane potential ($\Delta\psi m$) and the activity of the complexes of the ETC are highly interdependent [2]. Therefore dissipation of the mitochondrial membrane potential on one hand could lead to an increase in ROS generation when respiration is inhibited. On the other hand, if drop in the $\Delta\psi m$ is stimulated by uncoupling, it could lead to a reduced rate of free radical production. Similarly, hyperpolarisation of mitochondria could lead to an increase of ROS production. Thus, production of ROS in the ETC is dependent on the release of electrons out of the electron transport chain followed by the formation of free radicals. The process of release of electrons could be induced by reverse flux of electrons and activity of complex I and II as a donor of electrons and partial inhibition of the complexes by hyperpolarisation, ischaemic conditions or by chemical compounds [3;4] (Figure 1). Although hydrogen peroxide was a first ROS which was shown to be produced in mitochondria [5;6];[7], electron escape from ETC generate free radical predominantly in the form of super oxide radical $O_2^{\cdot -}$ which later converts to H_2O_2.

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Despite the fact that respiratory chain is a major ROS producer in mitochondria under resting conditions, several matrix proteins and complexes, including enzymes of TCA cycle such an aconitase, pyruvate dehydrogenase (PDH), and α-ketoglutarate dehydrogenase (αKGDH) could produce $O_2^{\cdot-}$ [8];[9]. Some inner mitochondrial membrane proteins (various cytochrome P450 enzymes, glycerol-3-phosphate dehydrogenase) which activity is partially dependent on $\Delta\psi m$ are also could produce ROS. Located on the outer membrane of mitochondria, enzyme monoamine oxidase (MAO) is utilizing monoamines producing aldehydes and hydrogen peroxide, another outer membrane protein cytochrome b5 reductase (Cb5R) which also can produce ROS (Figure 1).

Redox balance in the mitochondrial matrix is maintained by effective antioxidant system. Lifetime of the superoxide anion is 1 nanosecond and it can rapidly dismutate spontaneously or enzymatically with the help of manganese superoxide dismutase in mitochondrial matrix or by Cu, Zn-superoxide dismutase in the intermembrane space to hydrogen peroxide. Major endogenous antioxidant glutathione (GSH) is distributed through mitochondria and the rest of the cell and isolate major peptides from oxidation by $O_2^{\cdot-}$ or other forms of ROS. The permeable H_2O_2 is participating in signalling cascades and degraded by enzymes catalase (CAT), glutathione peroxidase (GPx), and peroxiredoxin 3 [10]; [11].

One of the major initial form of ROS in mitochondria is superoxide anion radical $O_2^{\cdot-}$. Considering very short lifetime of this free radical (~$1*10^{-9}$ second) it is very unlikely that superoxide can play role in physiology but possibly it can induce oxidative damage in neighbouring area. Superoxide dismutase (SOD1) is more likely play signalling rather antioxidative enzyme because it convert $O_2^{\cdot-}$ to more stable hydrogen peroxide which can be transported as signalling molecule (Figure 1). However, H_2O_2 can become dangerous for cells when it produce most toxic form of ROS – hydroxyl anion in Fenton reaction [12].

Mitochondria possess a number of “tools” to produce ROS in response to extracellular (such as the decrease of the oxygen level, toxins, increase of glucose uptake), cellular (hormones, transmitters), or intramitochondrial (availability of substrates) triggers. Mitochondrially generated ROS (from MAO) can stimulate lipid peroxidation which activates phospholipase C and IP3-triggered calcium signal [13]; [14]; [15] (Figure 1). Mitochondrial ROS increase in response to hypoxia stimulate calcium signal in astrocytes [16] and actives respiration [17]. Mitochondrial calcium uptake is redox sensible and can be regulated by ROS [18]. More prolonged elevation of ROS in mitochondria shown to be involved in the number of cell processes including proliferation of the cells [19]. However, any well balanced systems, even such a mitochondria, could be disrupted that result in pathology.

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Overproduction of ROS or dysregulation of antioxidant system lead to a number of pathologies, in brain it leads to cell death and neurodegeneration.

Neurodegenerative diseases are progressive, devastating and incurable, and are becoming increasingly prevalent in our aging populations. Aging of the population around world brings the neurodegenerative diseases to be one of the top medical and social problems. Thus, two major neurodegenerative disorders – Alzheimer's disease (AD) and Parkinson's Disease (PD) affecting 5% (AD) and 1 % (PD) of individuals aged 65 and above [20]; [21]. The annual cost in nursing home care for major neurodegenerative disorders in European countries is estimated to be in hundreds of million euros [22].

Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, motor neuron disease, and Huntington disease all share a several common feature such an accumulation of abnormally aggregated proteins termed pathological inclusions and involvement of oxidative damage and mitochondrial dysfunction in pathogenesis. Many of the genes associated with PD, ALS or ataxias are linked to mitochondria. All aggregated misfolded proteins which involved in neurodegenerative disorders (β-amyloid, tau, α-synuclein and huntingtin) inhibiting mitochondrial function and induce oxidative stress [23;24]. Importantly, mutations in mitochondrial DNA result not only in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), or myoclonic epilepsy with ragged red fibers (MERRF) but also to PD. Involvement of oxidative stress in the mechanism neuronal loss shown for the majority of neurodegenerative disorders [25]. However, antioxidant therapy approaches have failed as a treatment on a clinical level for the most of these diseases.

Although mitochondria produced far less ROS compare to NADPH oxidase, in long-lived neurons, where active mitochondria function must be maintained for an entire lifetime, implication of mitochondrial ROS in physiology and pathology may be crucial. Here we review the role of mitochondrial ROS in pathology of neurodegeneration.

Alzheimer's disease. Alzheimer's disease (AD) is a most common neurodegenerative disorder affecting aged population. Pathology of AD is characterised with senile plagues (consists predominantly with aggregated β-amyloid) and intracellular neurofibrillary tangles (formed by tau aggregates). The involvement of mitochondria in the mechanism of AD pathology is not so direct, when compared to other neurodegenerative disorders, but the role of oxidative stress and mitochondrial dysfunction is shown for diverse models of AD [24]. Thus, reduction in complex IV

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activity has been demonstrated in mitochondria from the hippocampus and platelets of AD patients and in AD cybrid cells [26;27] [1]. Aggregation of βA leads to oxidative stress, mitochondrial dysfunction and energy failure prior to the development of plaque pathology [28].

Aggregated βA can reduce of mitochondrial respiration in neurons and astrocytes through the inhibition of complexes I and IV [29];[30]. Inhibition of ETC potentially can induce ROS production but direct increase in mitochondrial ROS production was shown in relatively small amount of publication [31];[32]. However, superoxide production from mitochondria but not from NADPH oxidase shown to be associated with blocked long-term potentiation in Tg2576 mouse model of AD [33]. Importance of mitochondrial ROS was also confirmed by results with mitochondrially located antioxidant MitoQ, which prevented cognitive decline, Aβ accumulation, astrogliosis, and synaptic loss in triple transgenic mouse model of AD [34]. MitoQ extends lifespan and improves health span of a transgenic Caenorhabditis elegans model of Alzheimer disease [35]. The role of oxidative damage in sporadic AD is confirmed in experiments where inhibition of lipid peroxidation with deuterium-reinforced polyunsaturated fatty acids diet improve cognition and memory in in aldehyde dehydrogenase 2 (Aldh2) null mice, an established model of oxidative stress-related cognitive impairment that exhibits AD-like pathologies [36]. Olfactory bulbectomy lead to the strong AD phenotype in mice. In mice, neurodegeneration which caused by olfactory bulbectomy is accompanied by energy metabolism disturbances and oxidative stress in brain mitochondria similar to those occurring in transgenic animals - familial AD models and patients with sporadic AD [37].

Many cases of autosomal dominant early onset Alzheimer's disease (AD) result from mutations in the genes encoding in presenilins (PS1 or PS2). Mitochondrial ROS shown to be important in the mechanism of the triggering of mitochondrial permeability transition pore (PTP) and activation process of cell death in PS1 cells [38].

Mitochondrial ROS production in AD models is much smaller comparing to effects on the production of ROS in NADPH oxidase [39] [40]. However, production of ROS in NADPH oxidase lead to mitochondrial depolarisation due to lack of substrates due activation of the DNA-repairing enzyme PARP [41]; [42]; [43]. Combination of calcium and ROS production under β-amyloid stimulation induce opening mitochondrial PTP and cell death [44]; [45]; [46]. Prevention of PTP opening by inducing cyclophilin D deficiency (molecular blocker of PTP opening) is also able to improve mitochondrial function and learning/memory in an aging Alzheimer disease mouse model [47].

Oxidative stress is proven to be one of the major trigger for pathology in AD [1] but mitochondrial is shown to be a target for oxidative damage rather than source of ROS production.

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Familial form of frontotemporal dementia is induced by mutation in MAPT gene, encoding tau. Function of mitochondria is altered in the neurons of these patients. It results in the higher mitochondrial membrane potential with overproduction of the ROS in mitochondria, which in turn causes oxidative stress and cell death. Mitochondrial ROS overproduction in these cells is a major trigger for neuronal cell death and can be prevented by mitochondrial antioxidants [48].

Vascular diseases causing dementia. Vascular dementia is the cognitive decline resulting from cerebral vasculature hypoperfusion. A chronic hypoperfusion or blockade of a brain blood vessel could lead to a damage of the surrounding brain tissue and build-up of toxic waste substances and could result in various conditions, e.g. cerebral small vessel disease (CSVD) induced by hypercholesterolemia, cerebral amyloid angiopathy (CAA), stroke and ischaemia reperfusion injury, etc. Very often vascular dementia is a prerequisite for the development of Alzheimer's disease when a defect clearance of β- amyloid is present. Undeniably, all these conditions have the same output phenotype - impairment of mitochondrial function and increased oxidative stress due to chronic hypoxia and substrate deprivation. Oxidative stress and mitochondrial dysfunction has been linked to the development of dementia in majority of the cases [97]. Supplementation with last generation antioxidants Resveratrol in form of solid lipid nanoparticles or Edaravone has been very promising. This type of treatment could activate Nrf-2/ HO-1 pathway and could mitigate the mitochondrial ROS production, the consequent lipid peroxidation, protein carbonyls formation and to improve the Mn-SOD activity in a permanent bilateral common carotid artery occlusion rodent model of vascular dementia [98;99].

Parkinson's Disease. There is much evidence that oxidative stress occurs in, and contributes to, the pathogenesis of PD. Post mortem studies of the brains of patients with PD reveal increased levels of lipid peroxidation markers (malondialdehyde and 4-hydroxynonenal) and the presence of protein oxidative damage in the form of protein carbonyls [49]. It has been reported that there is an increase in the common deletions in mtDNA in the surviving dopaminergic neurons in the substantia nigra of patients with PD. These deletions are caused by oxidative stress [50]. Both the toxin and genetic models of PD also demonstrate increased oxidative stress which is connected with mitochondrial function. Inhibitors of mitochondrial complex I, rotenone or 1-methyl-4-phenylpyridinium (MPP+) produces superoxide anions in submitochondrial particles, and the neurotoxic effects of MPP+ and rotenone are probably caused by oxidative stress rather than metabolic changes because they can be can be effectively prevented by treatment with antioxidants [51]. Importantly, mutations in mitochondrial complex I lead to neurodegeneration. In neurons derived from stem cell cybrids that

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contain such mtDNA mutations, the major trigger for cell death is also overproduction of superoxide in the matrix of mitochondria, but not an energy deprivation [52]. Mild uncoupling of mitochondria with mitochondrial uncoupling protein-2 (UCP-2) overexpression reduces ROS production in toxic (MPP+, rotenone) mouse model of PD. UCP-2 deficiency also increases the sensitivity of dopamine neurons to MPTP, whereas UCP-2 overexpression decreases MPTP-induced nigral dopamine cell loss [53]. Mutations in Parkinson protein-1 (PARK-1, which is also known as DJ-1) cause a rare autosomal-recessive form of PD. Loss of function of DJ-1 results in oxidative stress, and DJ-1 exerts neuroprotection via its antioxidant mechanism in mitochondria [54] [55]. DJ-1 knockout mice demonstrate increased mitochondrial oxidant stress and downregulation of mitochondrial uncoupling proteins [56].

Mutations in PINK1 cause a recessive form of PD. PINK1 is a mitochondrial kinase, and we and other authors have previously demonstrated that PINK1 deficiency results in impaired respiration with inhibition of complex I, and rotenone-like increased production of ROS in mitochondria [57]; [58]. Fibroblasts from patients with PINK1-associated PD exhibit impaired oxidative phosphorylation and oxidative stress [59]; [60]. Excessive ROS production in mitochondrial of PINK1 knockout neurons can be an inductor of inhibition of mitochondrial Na^{2+}/Ca^{2+} exchanger or glucose transporter and can be rescued by antioxidants [57]; [61]; [62] (Figure 1). Activation of Nrf2 by pharmacological activators restore mitochondrial metabolism in PINK1 deficient cells [63]. Additional ROS production in monoamine oxidase under application of dopamine induce opening of mitochondrial PTP and cell death in PINK1 deficient neurons [64].

It should be noted, that mitochondrial ROS play important role in pathology of PINK1 (mutation or deficiency) but also in physiology of PINK1/Parkin related mitophagy. Mitochondrial ROS production has been shown to be important for induction of mitochondrial recruitment of Parkin and initiation of mitophagy [65].

Excessive ROS production in mitochondria the familial and sporadic form of PD damage DNA that activates DNAA repairing enzyme PARP which induce energy deprivation in neurons due to NAD consumption [66]; [67] (Figure 1). Both familial and sporadic forms of PD are characterised by forming of Lewy body which consists from aggregated α-synuclein. While monomeric α-synuclein play physiological role in synaptic transduction and mitochondrial bioenergetics [68] [69], oligomeric peptide become toxic for cells [23]. Oligomeric α-synuclein is detected in mitochondria [70] where it inhibit complex I [71];[72]. Despite the fact that α-synuclein induced oxidative stress can be quenched by application coenzyme Q10 [73], the effect of any form of α-synuclein on mitochondrial ROS production was not identified [74]. Oligomeric α-synuclein is producing ROS independently of

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known enzymatic pathways that affect mitochondrial function and induced lipid peroxidation [75]; [74].

Progressive Supranuclear Palsy (PSP) is a form of atypical Parkinsonism which is characterised by accumulation of 4R tau inclusions and classified as tauopathy. The microtubule associated protein tau (MAPT) H1 haplotype is the major genetic risk factor associated with PSP, but recently many genes encoding proteins important in mitochondrial function or oxidative stress management, e.g. debrisoquine 4-hydroxylase (CYP2D6), paraoxonase (PON) 1 and 2, N-acetyltransferase (NAT) 1 and 2, and superoxide dismutase (SOD) 1 and 2 have also been implicated [93]. This links to findings that mitochondrial dysfunction and excess mitochondrial ROS production, lipid peroxidation as early as it occurs in mesenchymal stem cells from patients with the sporadic form of PSP pointing towards essential contribution of the cellular pathology. Importantly, even in the early developmental status the MSCs exhibit metabolically dysfunctional mitochondria and this negatively influences their differentiation capacity [94] and thus obscures the hope for autologous transplantation of mitochondria as a possible therapeutic direction for this disease.

Amyotrophic Lateral Sclerosis (ALS). The role of mitochondrially driven oxidative stress is linked to familial form of ALS with mutation in mitochondrial superoxide dismutase (SOD1). Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease in which loss of spinal cord and cortical motor neurons starts leads to progressive paralysis and premature death [76];[77]. Mitochondrial oxidative damage has been demonstrated in patients affected by sporadic ALS [78]; [79] and in transgenic mice expressing a familial ALS-linked mutant Cu,Zn superoxide dismutase (SOD1) [80]. Importantly, reduction of the mitochondrial ROS in neurons with SOD1 mutant mouse model by generating double transgenic model with UCP2 (uncoupling protein 2) did not recover mitochondrial function and accelerates disease progression [81]. Mutations in RNA Transactivation response DNA-binding protein 43 (TDP-43), FUS/TLS and p62 are also associated with ALS and cells with these mutations also shown to have increase mitochondrial ROS and oxidative stress [82] [83].

Neurodegeneration with brain iron accumulation (NBIA). NBIA comprises of a heterogeneous group of diseases that a characterised by accumulation of iron in the basal ganglia and show mutation in PANK2 (pantothenate kinase). Pantothenate kinase (PANK2) mutation leads to a deficiency in CoA which in turn impairs energy metabolism in mitochondria. Acetyl CoA plays a role in synthesis and oxidation of fatty acids and oxidation of pyruvate in TCA. Animal models of the disease have failed so far because the rodent PANK-/- phenotype is not the typical neurodegenerative phenotype with brain iron accumulation and defective movements unless it is subjected to a ketogenic diet [85], the reason probably being the localisation of the murine PANK2 homolog is cytosolic in contrary to the

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human PANK2 that has been attributed to the mitochondria. Induced pluripotent stem cells (iPSC)-derived from PANK2 patient fibroblasts have been recently attempted to model the disease. These neurons have been shown to exhibit reduced glutathione levels and increased cytosolic and mitochondrial ROS production. Moreover, supplementation with CoA has been shown to be protective [86]. Similarly, in our PANK2 iPSC-based model defective mitochondrial Complexes I and II function, increased ROS production and lower levels of cellular GSH which further resulted in increased lipid peroxidation have been demonstrated [87]. Application with the iron chelator Desferal further increased ROS production and further exacerbate the PANK2 phenotype.

However, mutations in several genes have been known to cause neurodegeneration with brain iron accumulation, e.g. PLA2G6, C19orf12, COASY, FA2H, ATP13A2, FTL/FTL1 etc. [84] and importantly, most of them are connected to oxidative stress.

PLA2G6 mutation is an autosomal recessive mutation in the gene encoding the calcium-independent phospholipase A2 located to the chromosome 22q12-q13 leads to infantile neuroaxonal dystrophy (INAD). Recently it has been discovered that PLA2G6 mutation lead as well to neurodegeneration with brain iron accumulation (NBIA) [88]. It has been reported that PLA2G6 mutation leads to development of early onset Parkinsonism [89]. Earlier on, a discovery that links the pathology of neurodegeneration with brain iron accumulation phospholipid metabolism to the disruption brain iron homeostasis has been shown [88;89]. Mitochondrial dysfunction, increased mitochondrial ROS generation and lipid peroxidation in fibroblasts from patients with PLA2G6 mutation was reported. Importantly, feeding Drosophila iPLA2-VIA-/- flies with deuterated PUFAs reduced the rates of lipids peroxidation to basal as well as partially rescue their locomotor deficits [90].

Friedrich's ataxia (FRDA). Cerebellar ataxia is caused by a mutation in the FXN gene, which leads to a GAA repeat expansion and lower availability of the protein frataxin, a key component for the formation of the Fe-S clusters of the mitochondrial complexes I, II and III from the electron transport chain (ETC). Increased levels of mitochondrial (and cytosolic) ROS production and level of lipid peroxidation from cerebellar granule cells from FRDA granule cells [91] is due to a inhibition of the mitochondrial respiration complex I and abnormal accumulation of iron in the mitochondria. In fibroblasts from two FRDA mouse models, YG8R and KIKO, inhibition of lipid peroxidation with deuterated PUFAs and Nrf-2 activators, TBE31 and Sulforaphane, could prevent the lipid peroxidation damage and the consequent cell death in these cells [92].

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Huntington's disease (HD). HD-an autosomal dominant mutation of the mhtt gene, arises as a result a CAG repeat expansion of the gene coding the protein huntingtin. Similar to many other neurodegenerative diseases, oxidative stress and inflammation are heavily implicated. Characteristic for the HD brain samples are the increased levels of superoxide dismutase (Zn/Cu-SOD and mitochondrial Mn-SOD), glutathione peroxidases (GPx) and catalase (CAT), but not any canonical antioxidant response elements (AREs) gene products (NQO1, GCLM, GCLC, HMOX1/HO-1) [95]. However, neither overexpression of cytosolic Zn/Cu-SOD or mitochondrial Mn-SOD nor nutritional supplementation with α-tocopherol and coenzyme Q10 has led to prolongation of the lifespan of Drosophila HD model flies. In contrary, activation of the Nrf2 pathway by SIRT2 inhibition and induction of NQO1 has been very [promising and effective in protecting oxidative damage in rodent and human HD models [96].

Conclusions

Mitochondria extensively generate ROS or/and are targeted by free radicals in the aetiopathology of the major neurodegenerative diseases. In most of the diseases overproduction of ROS or loss of function of antioxidant pathways lead to oxidative damage of biological molecules. This in turn leads to a deregulation in the function they are responsible for or ultimately to the initiation of cell death. Thus, even small increase in ROS production over the basal rates requires elevated antioxidant activity. Maintenance of the major antioxidant systems (in brain predominantly GSH) is a highly energy consuming process and any increased activity of antioxidants production may lead to limitation of substrates for the normal functioning of mitochondria (Figure 2).

Mitochondrial redox balance and physiological role of mitochondrial ROS are very important in neuronal housekeeping. And despite the vast amount of publications which confirm damaging role of mitochondrial ROS in neurodegeneration, mitochondrially targeted antioxidants are not effective in treatment of neurodegenerative diseases on a patient level due various reasons, including quenching effect on the physiological signalling function of ROS. Antioxidant therapy has been proven to be effective for a number of neurodegenerative disorders in experiments on a cellular level, but most of the clinical trials have failed to demonstrate neuroprotection or efficacy in patients. This failure to translate the positive effects of antioxidants is usually attributed to the difficulties in antioxidant delivery to cells in the brain, or by the chemical instability of antioxidants. We propose that oxidative damage in neurodegeneration should be prevented or restricted through the direct inhibition of ROS production from specific sources, rather than through the use of scavengers. Furthermore finding the ways to quench the production of free radicals in these cells

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specifically, either through direct inhibition of an enzyme, or by increasing the endogenous antioxidants or by increasing energy production, represents one of the most promising directions of development for therapeutic strategies.

Figure Legends

Figure 1. Mitochondria is a producer and target of ROS. Mitochondria generating ROS in ETC, TCA cycle enzymes and monoamine oxidase (MAO). Production of hydrogens peroxide in MAO, or superoxide in ETC can stimulate lipid peroxidation and IP3 dependent calcium signal. Overproduction of ROS in NADPH oxidase in Parkinson's disease or Alzheimer's disease activates PARP which consume NAD and reduce NADH for complex I. Mitochondrial ROS production can inhibit glucose transporter and induce limitation of mitochondrial substrates for mitochondria.

Figure 2. Balance and interrelation between ROS production, energy metabolism and antioxidant homeostasis. Any changes in this balance lead to oxidative damage.

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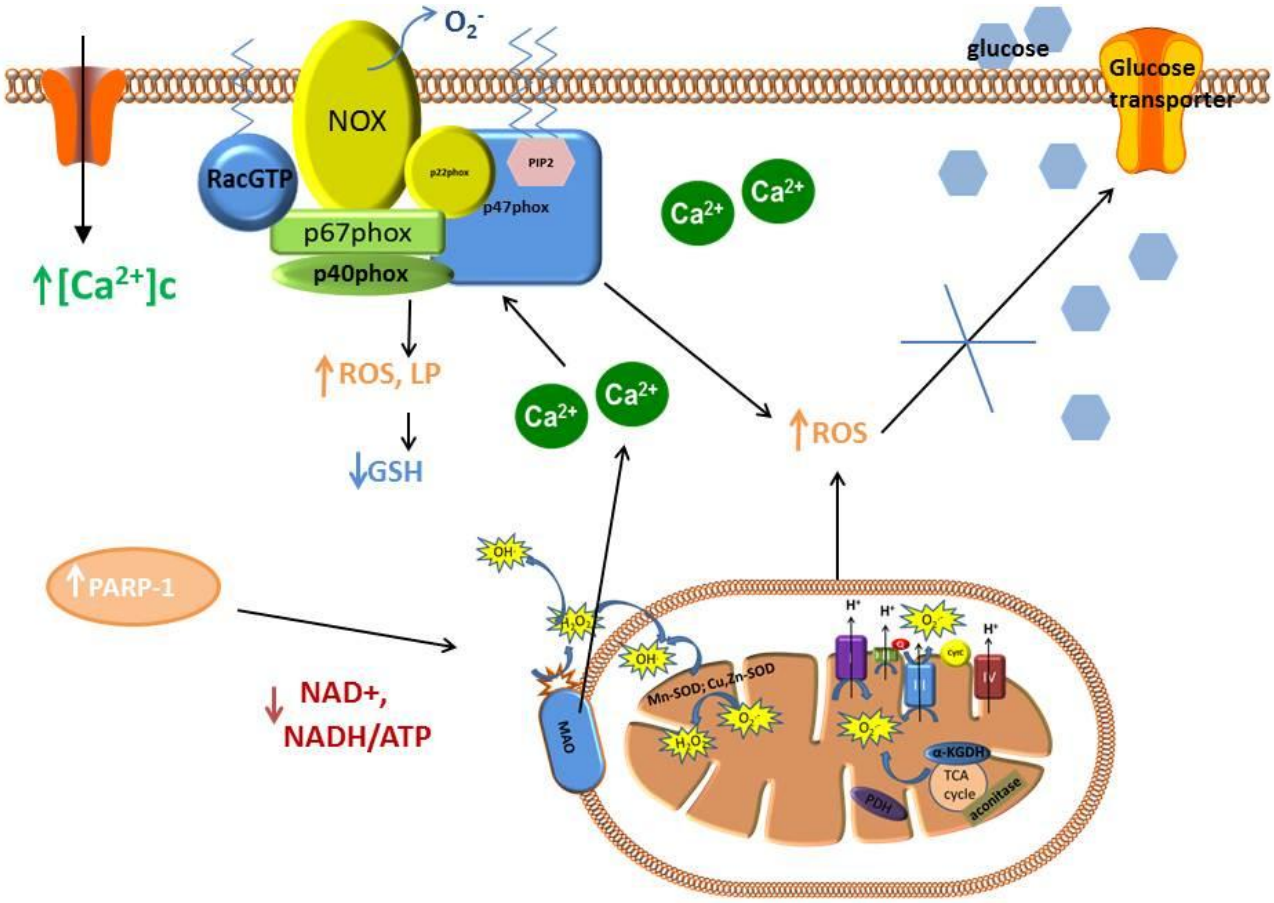

Figure 1

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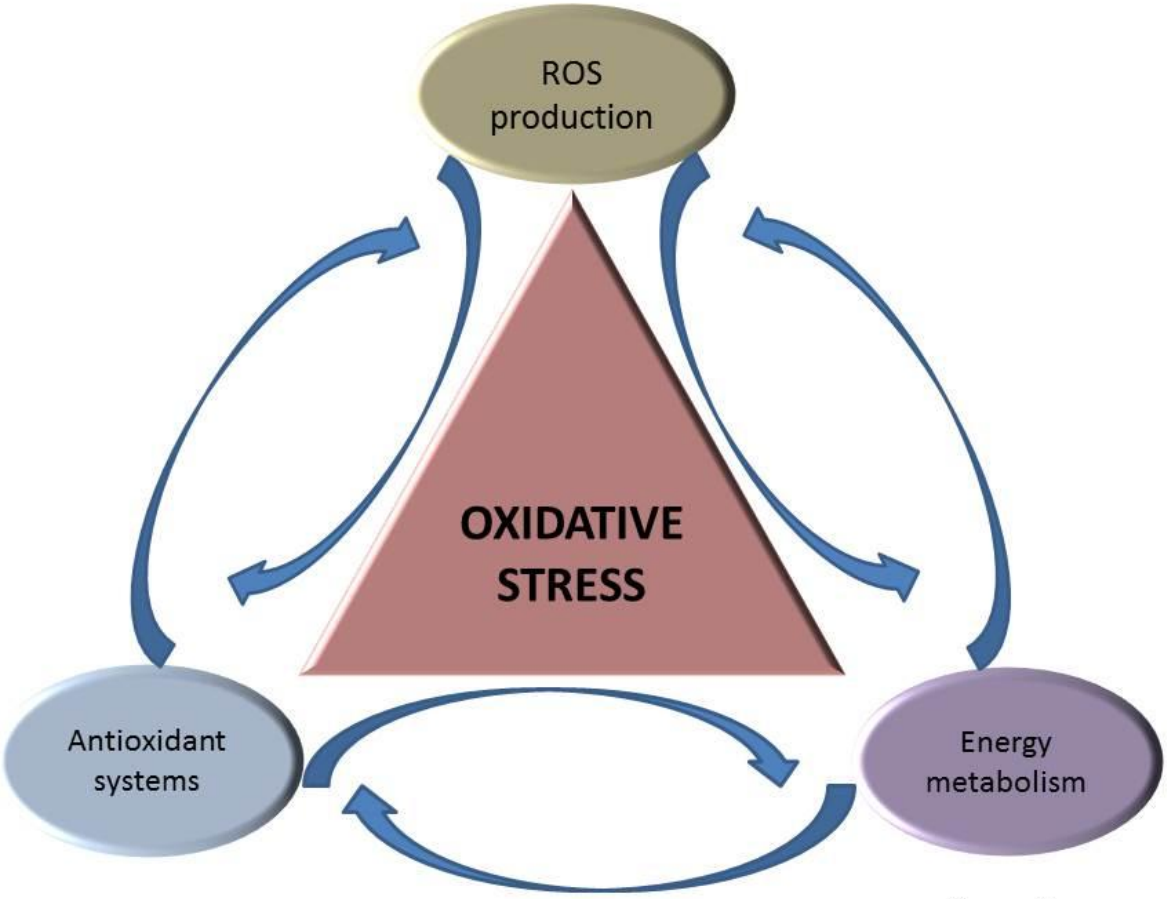

Figure 2

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